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Percutaneous Left Atrial Appendage Occlusion for Stroke Prophylaxis in Nonvalvular Atrial Fibrillation

CME

A Systematic Review and Analysis of Observational Studies

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CME Objective for This Article:

At the completion of this article, the learner should be able to: 1) evaluate alternatives to anticoagulation for stroke prophylaxis in patients with nonvalvular atrial fibrillation who have contraindications to anticoagulation; 2) compare the efficacy of percutaneous left atrial appendage occlusion devices to historical controls treated with anticoagulation for the prevention of stroke in patients with non-valvular atrial fibrillation; 3) compare the safety of percutaneous left atrial appendage occlusion devices to historical controls treated with anticoagulation for the prevention of stroke in patients with non-valvular atrial fibrillation; and 4) identify trials that study the PLAATO, Amplatzer, Watchman, and Lariat devices.

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Percutaneous Left Atrial Appendage Occlusion for Stroke Prophylaxis in Nonvalvular Atrial Fibrillation

A Systematic Review and Analysis of Observational Studies

Objectives The goal of this study was to provide a systematic review and analysis of observational studies on percutaneous left atrial appendage (LAA) occlusion for stroke prophylaxis in nonvalvular atrial fibrillation (NVAF).

Background A recent randomized controlled trial in patients with NVAF suggested noninferiority of percutaneous LAA occlusion versus medical management for stroke prevention. However, the use of percutaneous devices remains controversial because of limited literature on their efficacy and safety. We performed a systematic analytical review of existing observational studies to assess the rate of neurological events for patients treated with occlusion devices.

Methods A comprehensive search of the Medline, Scopus, and Web of Science databases from inception through August 1, 2013, was conducted using pre-defined criteria. We included studies reporting implantation in at least 10 patients and a follow-up of 6 months or more.

Results In 17 eligible studies, a total of 1,052 devices were implanted in 1,107 patients with 1,586.4 person-years (PY) of follow-up. The adjusted incidence rate of stroke was 0.7/100 PY (95% confidence interval [CI]: 0.3 to 1.1/100 PY), of transient ischemic attacks was 0.5/100 PY (95% CI: 0.1 to 1.8/100 PY), and of combined neurological events (strokes or transient ischemic attacks) was 1.1/100 PY (95% CI: 0.6 to 1.6/100 PY). Access site vascular complications and pericardial effusion were the most commonly observed procedural complications at a rate of 8.6% (95% CI: 6.3% to 11.7%) and 4.3% (95% CI: 3.1% to 5.9%), respectively.

Conclusions Our systematic review suggested comparable efficacy of LAA occlusion devices compared with historical controls treated with adjusted-dose warfarin and other anticoagulation strategies for prevention of stroke in patients with NVAF. (J Am Coll Cardiol Intv 2014;7:296–304)

Atrial fibrillation (AF) is the most common arrhythmia, affecting more than 5.5 million people in the United States alone (1–3). The lifetime risk of developing AF is reported to be as high as 26% for men and 23% for women (4). Stroke is a major contributor to morbidity and mortality among the U.S. population, affecting almost 800,000 patients every year. AF significantly increases the risk of ischemic stroke and is an underlying factor in up to 20% of total strokes among the elderly (5).

The left atrial appendage (LAA) is a remnant structure of the embryonic left atrium and persists as an out-pouching of the adult left atrial chamber. In a fibrillating atrium, the LAA becomes a major site of blood stasis, which significantly increases the risk of clot formation. Indeed, almost 15% of all patients with nonvalvular atrial fibrillation (NVAF) develop a thrombus in their heart, and transesophageal imaging studies have implicated the LAA as being the site for thrombogenesis in >90% of these cases (6,7). For this reason, stroke prophylaxis strategies and risk schema have been developed to determine which patients are at the highest risk for thromboembolic events. Therefore, anticoagulation with adjusted-dose warfarin or the newer anticoagulants has been offered to appropriate patients based on the accepted $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack) scoring system. However, anticoagulation increases the risk of both intracerebral and extracranial bleeding, and approximately 30% to 50% of patients with AF are ineligible to receive anticoagulation (5,8).

More recently, percutaneous LAA occlusion devices have been developed to overcome the aforementioned challenges in thromboembolic prophylaxis in patients with NVAF. The Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device (Appriva Medical, Plymouth, Minnesota) was the first to be tested and used in humans. Since then, multiple devices have emerged, including the Amplatzer device (AGA Medical Corporation/St. Jude Medical, Golden Valley, Minnesota), the Watchman device (Boston Scientific, Natick, Massachusetts), and the LARIAT suture delivery device (SentreHeart, Redwood City, California) (9–11) (Fig. 1). The only reported randomized clinical trial, PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation), has demonstrated noninferiority of the Watchman device to adjusted-dose warfarin therapy, and results from the CAP (Continued Access Protocol) registry following up on this trial suggest a decreasing trend of procedure-related complications as more

experience is gained with the technique (1,10). Although multiple observational studies have assessed the efficacy and safety of this novel technique, large-scale comparative data from clinical trials are not yet available. The results of the PREVAIL (Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) study and the ongoing AMPLATZER Cardiac Plug Clinical Trial are expected to produce more robust clinical evidence once they are reported. To that end, we performed a systematic statistical review of data pooled from the currently available observational studies to estimate the adjusted rates of stroke and major procedure-related complications. This type of analysis has the strength to provide a valuable estimate of the absolute effect of a particular intervention in the real-world scenario when enough comparator data from multiple randomized controlled trials or other comparative studies are not available (12).

Abbreviations and Acronyms

AF = atrial fibrillation

$CHADS_2$ = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack

CI = confidence interval

LAA = left atrial appendage

NNT = number needed to treat

NVAF = nonvalvular atrial fibrillation

PLAATO = Percutaneous Left Atrial Appendage Transcatheter Occlusion

PY = person-year(s)

TIA = transient ischemic attack

Methods

Search strategy. With the expertise of a medical librarian, we queried the Medline, Web of Science, and SCOPUS databases until August 1, 2013, for eligible studies with the following list of MeSH (Medical Subject Headings) terms: "atrial fibrillation," "atrial appendage," "left atrial appendage," "atrial fibrillation/prevention and control," "atrial fibrillation/surgery," "atrial fibrillation/therapy," "non valvular," "percutaneous," "minimally invasive," "transcutaneous," and "transcatheter."

Study characteristics. All observational studies, including case series and abstracts presented at scientific conferences, were considered. Of these, studies that reported outcomes after percutaneous closure in at least 10 patients with a minimum of 6 months follow-up were included. In instances where research groups reported cumulative results from multiple publications, caution was exercised in data extraction, and only studies with the largest sample size and follow-up period for each outcome were included (Fig. 1).

Outcome measures. The primary outcome was defined as the incidence of stroke in the follow-up period. Secondary outcomes included transient ischemic attacks (TIAs) and composite neurological events (defined as the combination of stroke and/or TIA) during the follow-up period. Safety outcomes including procedure failures and procedural/device-related complications were also analyzed. Procedural/device-related complications were defined as any of the following events: vascular access site hemorrhage, pericardial effusion or tamponade, device embolization, procedural mortality, and need for rescue cardiac surgery. Additionally, several subgroup analyses were performed to define the device characteristics that may predict the occurrence of stroke/TIA in the follow-up period. The number needed to treat (NNT) for stroke prevention was also calculated using the Newcombe-Wilson hybrid score (13).

Data extraction. The primary authors (N.S.B. and A.P.) searched all titles and associated abstracts using the described MeSH search strategy. Full-text papers for all potentially relevant studies were retrieved and reviewed with a primary focus on inclusion criteria, study outcomes, and methodological quality. If the clinical study met the inclusion criteria based on these 3 characteristics, it was included in the analysis. The data from the studies were then extracted using pre-designed structured forms and reviewed by 2 authors (S.A. and N.S.) for accuracy and validity. Disagreements, if any, were resolved by mutual consensus between the authors.

Statistical analysis. After the data elements were verified for accuracy, systematic and statistical analyses were conducted using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, New Jersey) and SAS version 9.3 (SAS Institute, Cary, North Carolina), respectively. Because of a relatively small proportion of primary events in each study, the data were assumed to follow a Poisson distribution. Pooled event rates (expressed as percentage per year) for the efficacy outcomes in the LAA arm and safety outcome rates (per 100 procedures) were calculated using standard methods. Fixed effects modeling was primarily utilized to conduct systematic analysis of included studies. However, we used random effects modeling in the case of statistically significant heterogeneity. Assessment of heterogeneity was achieved by comparing the inclusion/exclusion criteria and the minor differences in the design and conduct of the studies. We assessed for heterogeneity using the I^2 test (I^2 >50% with $p < 0.05$ implies significant heterogeneity). In cases of significant heterogeneity, the heterogeneity was first explored in the studies, and subsequently, analysis using a random effects model was performed to statistically account for the heterogeneity. Publication bias was assessed using the funnel plot method and corrected using the Duval and Tweedie trim and fill method (14).

Subgroup analyses were performed to determine event rates in different strata of the study population. All subgroup analyses were pre-specified. All of the p values were 2-tailed, with statistical significance specified at $p < 0.05$ and confidence intervals (CIs) computed at the 95% level. The analysis has been reported in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (15).

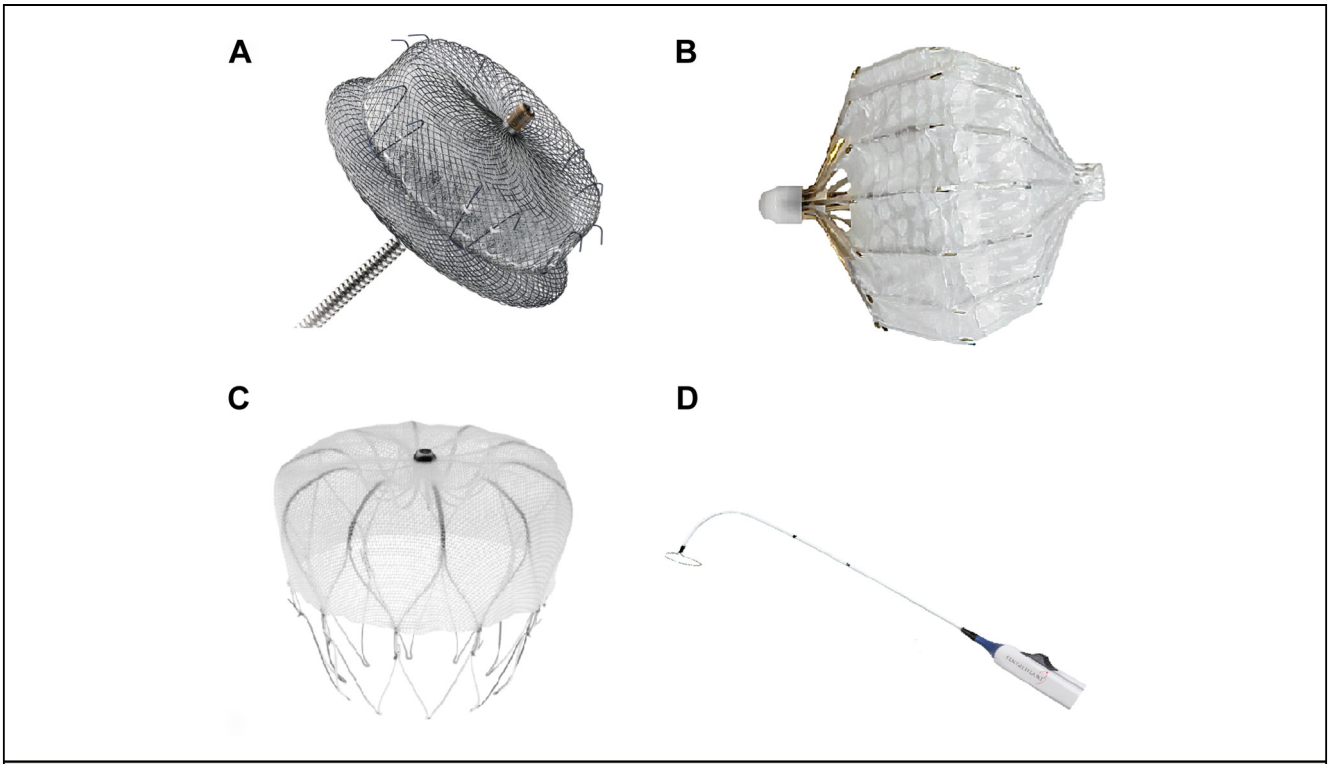

Figure 1. Devices Used for LAA Closure

(A) Amplatzer Cardiac Plug device. **(B)** Percutaneous Left Atrial Appendage Transcatheter Occlusion device. **(C)** Watchman device. **(D)** LARIAT device. LAA = left atrial appendage. Images were acquired from the websites of the following companies, with permission: Appriva Medical, AGA Medical Corporation/St. Jude Medical, Boston Scientific, and SentreHeart.

Results

We included 17 observational studies (16–30) for the final analysis in accordance with study inclusion criteria (Fig. 2). A total of 1,052 devices were implanted in 1,107 patients. The pooled analysis yielded 1,586.4 person-years (PY) of follow-up. Table 1 demonstrates the baseline characteristics of the included studies. The follow-up varied from 7 to 29 months among the studies. The mean $CHADS_2$ score was 2.7. Two studies had a mean $CHADS_2$ score of <2, and another 2 studies did not report $CHADS_2$.

The predicted stroke rate varied between 2.5 and 5.3/100 PY, assuming a $CHADS_2$ score of 3. Nine of 17 studies reported post-procedural utilization of antiplatelet agents (aspirin ± clopidogrel) for varying time periods. There were minor differences observed among inclusion and baseline characteristics of included studies as demonstrated in Table 1.

Efficacy outcomes. The actual procedural success was 1,052 of 1,107 (95.1%). The adjusted procedural failure rate was 8.4% (95% CI: 6.6% to 10.6%) using random effects modeling and adjusting for publication bias. The adjusted pooled incidence rate of stroke in our systematic analyses was 0.7/100 PY (95% CI: 0.3 to 1.1/100 PY) (Fig. 3). There was no publication bias to the right of mean, which was assessed using the Duval and Tweedie trim and fill method (Fig. 4). Table 2 demonstrates subgroup analyses by device type, year, and region; similar stroke rates were observed in the Watchman and PLAATO devices of 0.7/100 PY (95% CI: 0.0 to 1.5/100 PY) and 0.7/100 PY (95% CI: 0.0 to 1.6/100 PY), respectively, as compared with Amplatzer 0.9/100 PY (95% CI: 0.7 to 2.4/100 PY), although the difference was not statistically significant. There was no statistically significant difference observed in stroke rate over the year or region (Table 2). The NNT for 1 stroke was estimated at 21.7 (95% CI: 16.1 to 31.5) assuming a $CHADS_2$ score of 3 for the pooled population.

The adjusted rate of TIAs was observed to be 0.5/100 PY (95% CI: 0.1 to 0.8/100 PY), with an estimated NNT of 23.3 (95% CI: 16.9 to 35.5). The pooled composite rate of neurological events across all studies was found to be 1.1/100 PY (95% CI: 0.6 to 1.6/100 PY) (Fig. 2, Table 3) with a NNT of 25.0 (95% CI: 17.7 to 40.4).

Safety outcomes. Tables 4 and 5 demonstrate the adjusted pooled rates of periprocedural adverse events per 100 procedures observed across the studies. We calculated a combined adverse event rate of 16.0% (95% CI: 13.6% to 18.7%). There were no statistically significant differences in

the combined rate of complications over time (Table 5). Subgroup analyses revealed a higher rate of combined adverse events with both the Amplatzer and the Watchman devices (23.5% [95% CI: 15.9% to 33.2%] and 13.6% [95% CI: 9.7% to 18.8%], respectively), as compared with 5.4% (95% CI: 3.5% to 8.2%) for PLAATO and 7.3% (95% CI: 2.7% to 18.3%) for LARIAT devices, although these were not statistically significant. The most frequent complication was of the vascular access site: 8.6% (95% CI: 6.3% to 11.7%). The other frequently observed procedural complications were pericardial effusions and device embolization, which occurred at a rate of 4.3% (95% CI: 3.1% to 5.9%) and 3.9% (95% CI: 2.7% to 5.6%), respectively (Table 4).

Comparison with other anticoagulation strategies reported in the literature. Figure 5 demonstrates the rates of ischemic stroke despite therapeutic anticoagulation, as reported in the literature. In our review, the stroke rate with percutaneous LAA occlusion was estimated at 0.7/100 PY (95% CI: 0.2 to 1.2/100 PY), which is similar to recently reported results: preliminary data of the PREVAIL study (31) (reporting a stroke rate of 0.7/100 PY [95% CI: 0.1 to 5.1/100 PY]) and the PROTECT-AF study (10) (2.2/100 PY [95% CI: 1.3 to 3.5/100 PY]) and to other anticoagulation strategies, including adjusted-dose warfarin (32–35).

Discussion

Stroke prophylaxis poses a major challenge for patients with NVAF who have contraindications to anticoagulation. The LAA is the most common site for clot formation; therefore, surgical ligation of the LAA is widely practiced in patients undergoing open heart mitral valve surgery (36).

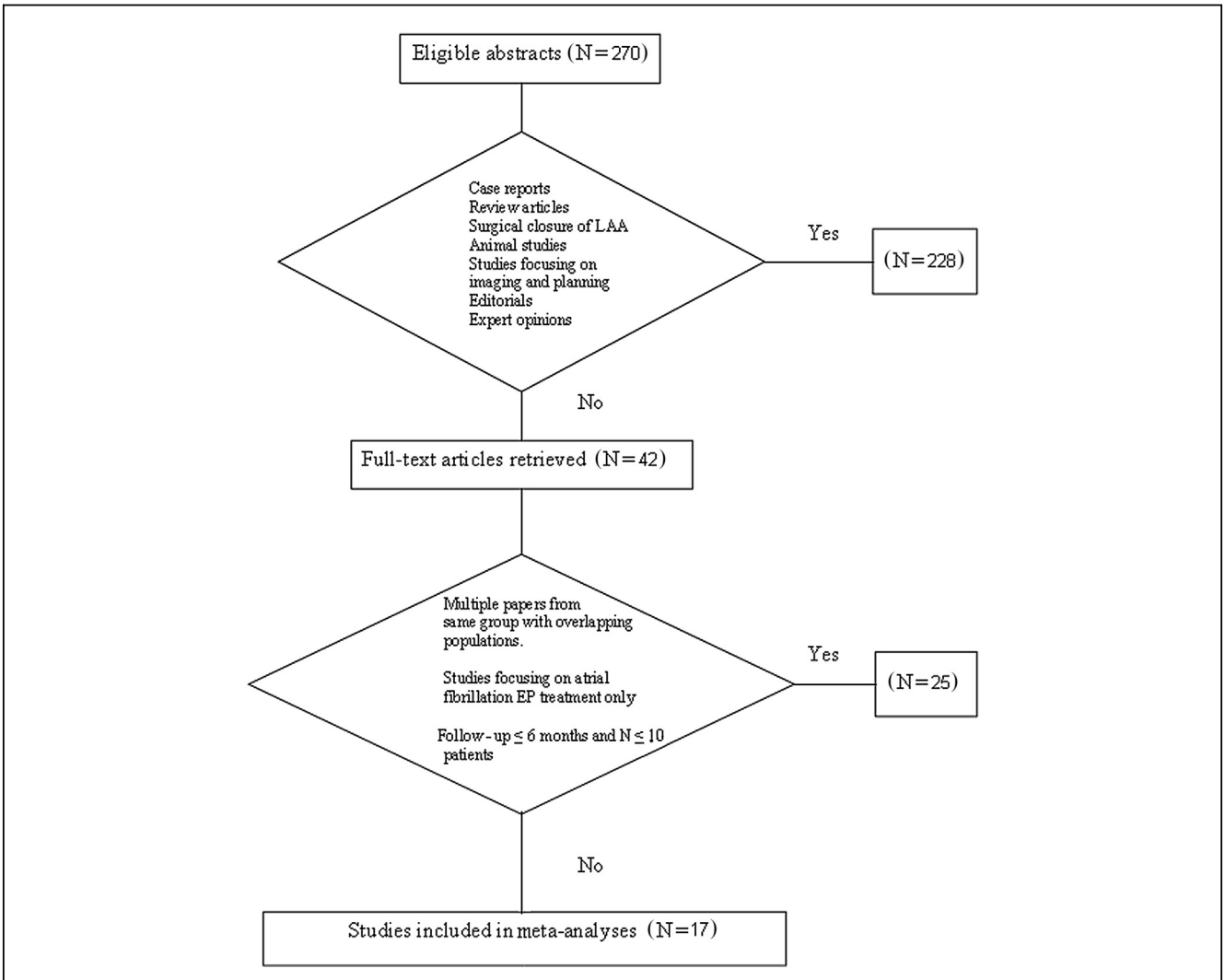

Figure 2. Flow Diagram Showing Selection of Studies for Analysis

EP = electrophysiology; LAA = left atrial appendage.

Table 1. Baseline Characteristics of Included Studies

First Author, Year (Ref. #)	Patients/ Devices	Follow-Up (months)	Device Used	Age (yrs)	$CHADS_2$	Hypertension	Diabetes Mellitus	Prior Stroke	Congestive Heart Failure
Ostermayer, 2005 (16)	111/108	9.8	PLAATO	71 ± 9	2.5	80 (72.1)	29 (26.1)	42 (37.8)	43 (38.7)
Himbert, 2006 (17)	11/9	7	PLAATO	72 ± 9	NR	NR	NR	NR	NR
Sick, 2007 (18)	75/66	24	Watchman	68.5/NR	1.8	55 (73.3)	22 (29.3)	NR	NR
De Meester, 2008 (19)	10/9	21	PLAATO	73 ± 5	3.3	NR	NR	NR	NR
Park, 2009 (20)	73/73	24	PLAATO	72.7 ± 9.7	2.5	69 (94.5)	26 (35.6)	25 (34.2)	NR
Ussia, 2009 (21)	20/18	40	PLAATO + Amplatzer	69 ± 8	3.0	18 (45.0)	11 (55)	12 (60.0)	8 (40.0)
Bayard 2010 (9)	180/162	8.6	PLAATO	70 ± 9.7	3.1	150 (83.3)	52 (28.9)	106 (58.8)	75 (41.7)
Lam, 2011 (22)	20/19	12.7	Amplatzer	68 ± 9	2.3	15 (75.0)	9 (45.0)	6 (30.0)	3 (15.0)
Bai, 2012 (23)	58/58	25.9	Watchman	74 ± 9	2.2	NR	NR	NR	NR
Reddy, 2013 (24)	150/142	14.4	Watchman	72.5 ± 7.4	2.8	142 (94.6)	48 (32.0)	61 (40.7)	43 (28.7)
Massumi, 2013 (25)	21/20	11.7	Lariat	73 ± 8	3.2	NR	NR	10 (47.6)	NR
Urena, 2013 (26)	52/51	20	Amplatzer	74 ± 8	3.0	48 (92.3)	21 (40.4)	32 (61.5)	10 (19.2)
Faustino, 2013 (27)	23/22	12	Amplatzer	70 ± 9	3.2	NR	NR	NR	NR
Danna, 2013 (28)	37/34	12	Amplatzer	73.4 ± 8.3	3.1	28 (75.7)	17 (45.9)	6 (16.2)	NR
Bartus, 2013 (11)	89/85	12	Lariat	62 ± 10	1.9	84 (94.3)	9 (10.1)	22 (24.7)	11 (12.4)
Nietlispach, 2013 (29)	152/152	32	Amplatzer + others	72 ± 10	NR	114 (75.0)	5 (9.6)	15 (10.0)	6 (3.9)
Helsen, 2013 (30)	25/24	29	PLAATO + Amplatzer	73 (49–85)	3.0	19 (76.0)	5 (17.2)	15 (60.0)	6 (24)

Values are n/n, mean, mean ± SD, n (%), or median age (range).

$CHADS_2$ = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack; NR = not reported; PLAATO = Percutaneous Left Atrial Appendage Transcatheter Occlusion.

Physiologically, percutaneous LAA occlusion should offer the same advantage, and hence, percutaneous closure device use is an interesting alternative in these patients. However, there is a paucity of clinical evidence behind the efficacy and safety of percutaneous LAA occlusion devices. Thus, we performed the first reported systematic review of pooled observational studies to compile the available contemporary evidence.

We estimated the rate of ischemic stroke to be 0.7/100 PY, which is similar to the preliminary PREVAIL trial data, but less than the rate reported in the PROTECT-AF trial (10). The estimated stroke rate in our study was either less

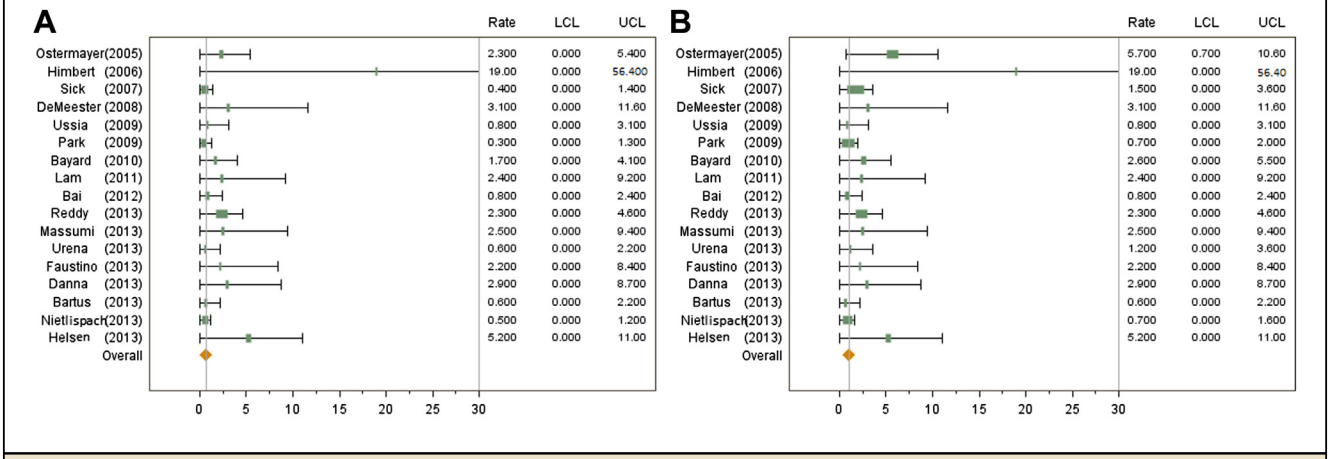

Figure 3. Forest Plots Depicting Stroke Rates and Composite Neurological Events Across Included Studies

(A) Incidence of stroke rate across studies per 100 person-years. **(B)** Incidence of total neurological events across studies per 100 person-years. LCL = lower confidence limit; UCL = upper confidence limit.

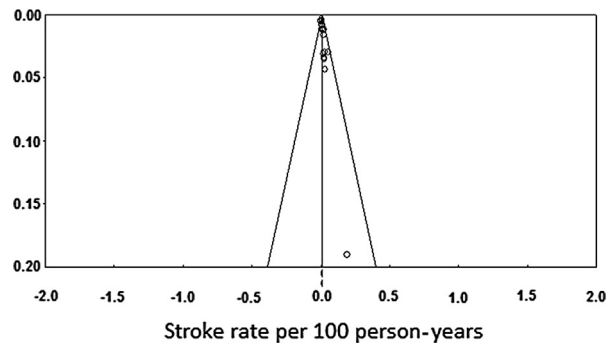

Figure 4. Publication Bias Assessed by Funnel Plot of Standard Error by Rate for Primary Outcome (Stroke)

than or comparable to contemporary strategies utilizing pharmacotherapeutic anticoagulation, suggesting non-inferiority of the percutaneous device implantation (10,32–35). We observed a procedure failure rate of 8.4% among all 4 implanted devices, which was comparable to the rate observed in the PROTECT-AF trial (9.1%), CAP registry (5.7%), and preliminary PREVAIL trial data available online (4.9%) (1,31). The rate of any complication was calculated to be 7.1% for all device types and 13.6% in the Watchman device subgroup, which seemed to be higher than what was observed in the PROTECT-AF trial (8.7%), CAP registry (4.1%), and preliminary PREVAIL trial (4.1%) data. We observed access site complications to be most common (8.6%), followed by pericardial effusion (4.1%), which is comparable to the PROTECT-AF trial data that showed these rates to be 3.5% and 4.8%, respectively. We observed no difference in pooled stroke rates with various device types, year, or region. There was no difference in procedural complications by device type. The comparison of pooled efficacy and safety outcomes by device type has not been reported in the literature thus far. The pooled rates of efficacy and safety outcomes of percutaneous LAA occlusion in observational studies look similar, if not better, than the PROTECT-AF trial data, indicating that the percutaneous LAA closure strategy could be a feasible option for stroke prophylaxis in the real world.

Table 2. Adjusted Pooled Rates of Stroke by Device Type, Year, and Region

Subgroups	Number of Studies	Adjusted Stroke Rate	95% CI Lower Limit	95% CI Upper Limit
Device type				
Amplatzer	3	0.9	0.7	2.4
PLAATO	5	0.7	0	1.5
Watchman	3	0.7	0	1.6
Lariat	2	0.7	0	2.3
Multiple	4	0.6	0	1.3
Year				
2005	1	2.3	0	5.4
2006	1	1.9	0	5.6
2007	1	0.4	0	1.4
2008	1	6.1	0	11.6
2009	2	0.4	0	1.3
2010	1	1.7	0	4.1
2011	1	2.4	0	9.2
2012	1	0.8	0	2.4
2013	8	0.7	0.2	1.3
Region				
Asia	1	2.4	0	9.2
Europe	9	0.6	0.1	1.1
Multicenter including United States	4	0.8	0	1.6
United States	2	0.9	0	2.4
Canada	1	0.6	0	2.2

Values are the incidence rate per 100 person-years.
CI = confidence interval; PLAATO = Percutaneous Left Atrial Appendage Transcatheter Occlusion.

Table 3. Adjusted Pooled Rate of Efficacy Outcomes

Event Type	Adjusted Pooled Rate	95% CI Lower Limit	95% CI Upper Limit
Stroke	0.7	0.3	1.1
Transient ischemic attack	0.5	0.1	0.8
Combined neurological events	1.1	0.6	1.6

Values are the incidence rate per 100 person-years.
CI = confidence interval.

Study limitations. The choice of medical therapy versus percutaneous LAA closure is dependent on whether the patient has any contraindication for medical therapy, which inherently creates a selection bias. Systematic pooling of

Table 4. Periprocedural Adverse Event Rates

Adverse Event	Adjusted Rate	95% CI Lower Limit	95% CI Upper Limit
Access site complications	8.6	6.3	11.7
Pericardial effusion	4.3	3.1	5.9
Pericardial tamponade	2.2	1.4	3.4
Device embolization	3.9	2.7	5.6
Procedural mortality	1.2	0.6	2.2
Need for surgery post-procedure	2.3	1.5	3.6
Procedural failure	8.4	6.6	10.6
All-cause mortality	6.6	5.1	8.4
Any of the above events by device			
Overall	16.2	13.8	18.9
Amplatzer, 3	23.5	15.9	33.2
PLAATO, 5	5.4	3.5	8.2
Watchman, 3	13.6	9.7	18.8
Lariat, 2	7.3	2.7	18.3
Multiple, 4	18.8	13.8	25.1

Values are the adjusted rate per 100 procedures.
Abbreviations as in Table 2.

Table 5. Periprocedural Adverse Event Rates by Year

Any Adverse Event (Year, Number of Studies)	Adjusted Rate	95% CI Lower Limit	95% CI Upper Limit
2005, 1	6.3	3	12.6
2006, 1	9.1	1.3	43.9
2007, 1	22.7	14.6	33.5
2008, 1	4.5	0.3	44.8
2009, 2	5.4	2.3	12.3
2010, 1	4.4	2.2	8.6
2011, 1	15	4.9	27.6
2012, 1	1.7	0.2	11.2
2013, 8	15.8	13.5	20.8

Values are the adjusted rate per 100 procedures.
CI = confidence interval.

different observational studies with different baseline characteristics may introduce some imprecision in the results as a result of heterogeneity. Several studies included in the systematic analysis have small numbers or have short follow-up periods. Because of the relative rarity of strokes and safety outcomes after percutaneous closure, recurrent events are more likely to be observed in larger study samples with a longer follow-up period. Another limitation arises from the fact that the included studies were conducted over different time periods in different countries utilizing different devices. It has to be taken into consideration that diagnosis and treatment modalities, including referral patterns, might have changed over time. Also, the event rates in observational studies are under-reported compared with randomized controlled trials. Despite these limitations, our review seeks to clarify extensive and confusing published data, by systematic organization and aggregation of available information.

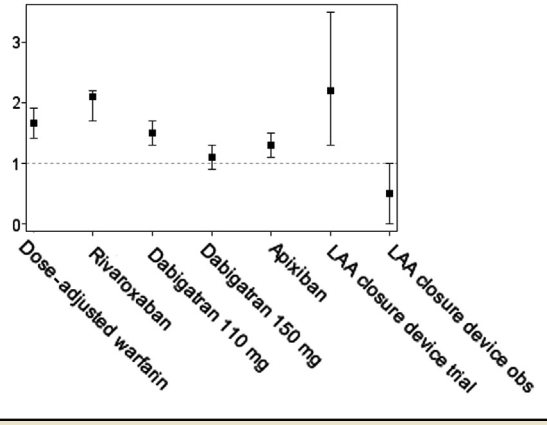

Figure 5. Comparison of Stroke Prophylaxis Strategies in NVAF

The **x-axis** represents treatment modalities, and the **y-axis** represents incident rate per 100 person-years with 95% confidence intervals. LAA = left atrial appendage; NVAF = nonvalvular atrial fibrillation; obs = observational trial.

Conclusions

In our systematic review and analysis, percutaneous LAA occlusion for stroke prophylaxis was comparable to historical controls for adjusted-dose warfarin and comparable to other anticoagulation agents, providing evidence for device utilization in NVAF patients unable to receive long-term anticoagulation. Needless to say, more randomized trials are required to conclusively compare LAA occlusion to current medical management strategies.

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REFERENCES

1. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) clinical trial and the Continued Access registry. Circulation 2011;123:417–24.
2. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455–61.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.
4. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042–6.
5. Landmesser U, Holmes DR Jr. Left atrial appendage closure: a percutaneous transcatheter approach for stroke prevention in atrial fibrillation. Eur Heart J 2012;33:698–704.
6. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755–9.
7. Manning WJ, Silverman DI, Gordon SP, Krumholz HM, Douglas PS. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. N Engl J Med 1993;328:750–5.
8. Gangireddy SR, Halperin JL, Fuster V, Reddy VY. Percutaneous left atrial appendage closure for stroke prevention in patients with atrial fibrillation: an assessment of net clinical benefit. Eur Heart J 2012;33:2700–8.
9. Bayard YL, Omran H, Neuzil P, et al. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. EuroIntervention 2010;6:220–6.
10. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009;374:534–42.
11. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108–18.
12. Agarwal S, Bajaj NS, Kumbhani DJ, Tuzcu EM, Kapadia SR. Meta-analysis of transcatheter closure versus medical therapy for patent foramen ovale in prevention of recurrent neurological events after presumed paradoxical embolism. J Am Coll Cardiol Intv 2012;5:777–89.
13. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873–90.
14. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.

15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
16. Ostermayer SH, Reisman M, Kramer PH, et al. Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. J Am Coll Cardiol 2005;46:9–14.
17. Himbert D, Cachier A, Brochet E, et al. [Feasibility of percutaneous exclusion of the left atrial appendage: results of 11 cases] (in French). Arch Mal Coeur Vaiss 2006;99:585–92.
18. Sick PB, Schuler G, Hauptmann KE, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2007;49:1490–5.
19. De Meester P, Thijs V, Van Deyk K, Budts W. Prevention of stroke by percutaneous left atrial appendage closure: short term follow-up. Int J Cardiol 2010;142:195–6.
20. Park JW, Leithäuser B, Gerk U, Vrsansky M, Jung F. Percutaneous left atrial appendage transcatheter occlusion (PLAATO) for stroke prevention in atrial fibrillation: 2-year outcomes. J Invasive Cardiol 2009; 21:446–50.
21. Ussia GP, Mulè M, Cammalleri V, et al. Percutaneous closure of left atrial appendage to prevent embolic events in high-risk patients with chronic atrial fibrillation. Catheter Cardiovasc Interv 2009;74:217–22.
22. Lam YY, Yip GW, Yu CM, et al. Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. Catheter Cardiovasc Interv 2012;79: 794–800.
23. Bai R, Horton RP, DI Biase L, et al. Intraprocedural and long-term incomplete occlusion of the left atrial appendage following placement of the WATCHMAN device: a single center experience. J Cardiovasc Electrophysiol 2012;23:455–61.
24. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). J Am Coll Cardiol 2013;61:2551–6.
25. Massumi A, Chelu MG, Nazeri A, et al. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. Am J Cardiol 2013;111:869–73.
26. Urena M, Rodés-Cabau J, Freixa X, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. J Am Coll Cardiol 2013;62:96–102.
27. Faustino A, Paiva L, Providência R, et al. Percutaneous closure of the left atrial appendage for prevention of thromboembolism in atrial fibrillation for patients with contraindication to or failure of oral anticoagulation: a single-center experience. Rev Port Cardiol 2013;32:461–71.
28. Danna P, Proietti R, Sagone A, et al. Does left atrial appendage closure with a cardiac plug system reduce the stroke risk in nonvalvular atrial fibrillation patients? A single-center case series. Pacing Clin Electrophysiol 2013;36:347–53.
29. Nietlispach F, Gloekler S, Krause R, et al. Amplatzer left atrial appendage occlusion: single center10-year experience. Catheter Cardiovasc Interv 2013;82:283–9.
30. Helsen F, Nuyens D, De Meester P, Rega F, Budts W. Left atrial appendage occlusion: single center experience with PLAATO LAA Occlusion System(®) and AMPLATZER™ Cardiac Plug. J Cardiol 2013;62:44–9.
31. PREVAIL Study: Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy. Boston Scientific website. Available at: http://www.bostonscientific.com/watchman-eu/.
32. Connolly SJ, Ezekowitz MD, Yusuf S, et al., RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
33. Patel MR, Mahaffey KW, Garg J, et al., ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
34. Granger CB, Alexander JH, McMurray JJ, et al., ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.
35. Agarwal S, Hachamovitch R, Menon V. Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis. Arch Intern Med 2012; 172:623–31.
36. Madden JL. Resection of left auricular appendix: a prophylaxis for recurrent arterial emboli. JAMA 1949;140:769–72.

Key Words: closure devices ■ left atrial appendage occlusion ■ nonvalvular atrial fibrillation ■ stroke ■ systematic analysis.

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